

**International
Waldenstrom's
Macroglobulinemia
Foundation**

IWMF



A Beacon of Hope • Giving Support • Searching for a Cure

Peripheral neuropathy (PN)

- **damage or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected**
 - **chronic: long term, begins subtly and progresses slowly**
 - **acute : sudden onset, rapid progress and slow resolution**
- **sensory nerves, motor nerves, autonomic nerves**

Neuropathy classification

- neuropathy affecting just one nerve is called “mononeuropathy”
- neuropathy involving multiple nerves in roughly the same areas on both sides of the body is called "symmetrical polyneuropathy"
- two or more separate nerves in disparate areas of the body are affected is called " mononeuritis multiplex” or multifocal mononeuropathy" or "multiple mononeuropathy“.

Prevalence of PN

- Osteosclerotic myeloma (POEMS) 50-85%
- **WM 30-50%**
- MGUS 5-37%
- Amyloidosis (AL) 10-20%
- Cryoglobulinemia 7-15%
- Multiple myeloma 3-14%
- Lymphoma 2-8%

Signs and symptoms

- **sensory function “negative” symptoms:**
 - **numbness to touch and vibration,**
 - **reduced sensitivity to temperature change and pain,**
 - **reduced position sense causing poor coordination and balance, and gait abnormality**
- **sensory function “positive” symptoms:**
 - **tingling, itching, crawling, pins and needles**
 - **pain or skin allodynia (severe pain from normally non-painful stimuli, such as light touch).**

Signs and symptoms

- **motor function “negative” symptoms (loss of function):**
 - **impaired balance and coordination**
 - **weakness and tiredness**
 - **heaviness and gait abnormalities**
- **motor function “positive” symptoms (gain of function):**
 - **cramps**
 - **tremors**
 - **muscle twitches (fasciculations)**

Signs and symptoms

- **autonomic nerve dysfunction:**
 - **poor bladder control**
 - **abnormal blood pressure or heart rate**
 - **reduced ability to sweat normally**
- **pain in the muscles (myalgias)**
- **Neuropathy may cause muscle loss, bone degeneration, and changes in the skin, hair, and nails.**

Mechanism of neuropathy

- **Mono, multi, cranial neuropathy & radiculopathy**
 - **direct infiltration**
 - **nerve/root compression**
 - **hyperviscosity**
 - **bleeding diathesis**
 - **cryoglobulinemia**
- **Symmetric polyneuropathy**
 - **Amyloidosis**
 - **chemo/drug related toxicity**
 - **M-protein reactivity with nerve (*IgM*)**
 - **unknown**

Anti-neural antigens of IgM

Antigens	% PN
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- | | |
|----------------|-----|
| ○ MAG | 50% |
| ○ Sulfatide | 6% |
| ○ GQ1b+Disyalo | 2% |
| ○ GD1a | 3% |
| ○ GM2 | 2% |
| ○ GM1 | <2% |

TREATMENT OF PN

- ***Patients not impaired in their daily life:***
 - symptomatic therapy for tremor and paresthesias
 - reassurance on the usually good prognosis for several years
- ***Slightly impaired patients:***
 - due to its safe profile and efficacy plasma exchange is probably preferred as first line treatment or during worsening / flare-ups
- ***Moderately impaired patients:***
 - Immunotherapy and/or chemo therapy
 - Rituximab is currently probably the preferred 1st line option.

Therapy of anti-MAG IgM PN

- Rituximab (62%)
- Plasma exchange (45%)
- Chlorambucil (40%)
- Steroids (39%)
- Cyclophosphamide (47%)
- IVIg (18%)
- Interferon α (27%)
- Fludarabine (52%)
- Other therapies (14%)

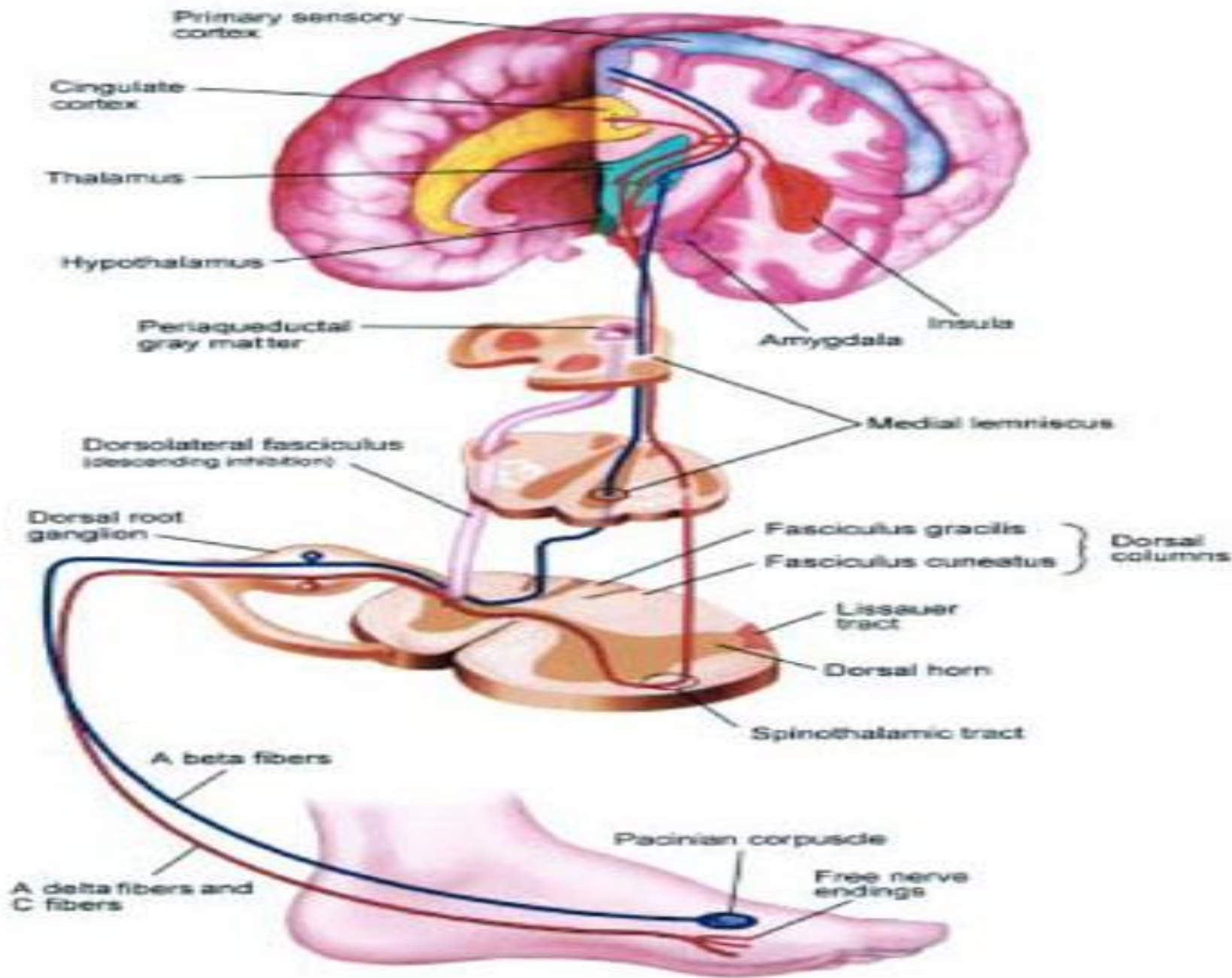
Immunotherapy for anti-MAG IgM PN

***The Cochrane Library* Reviewers' conclusions:**

- There is inadequate reliable evidence from trials of immunotherapies in anti-MAG neuropathy to recommend any particular immunotherapy.
- IVIg is relatively safe and may produce some short-term benefit.
- Large randomized trials of at least 12 months duration are required to assess the efficacy of existing or novel therapies.

PAIN

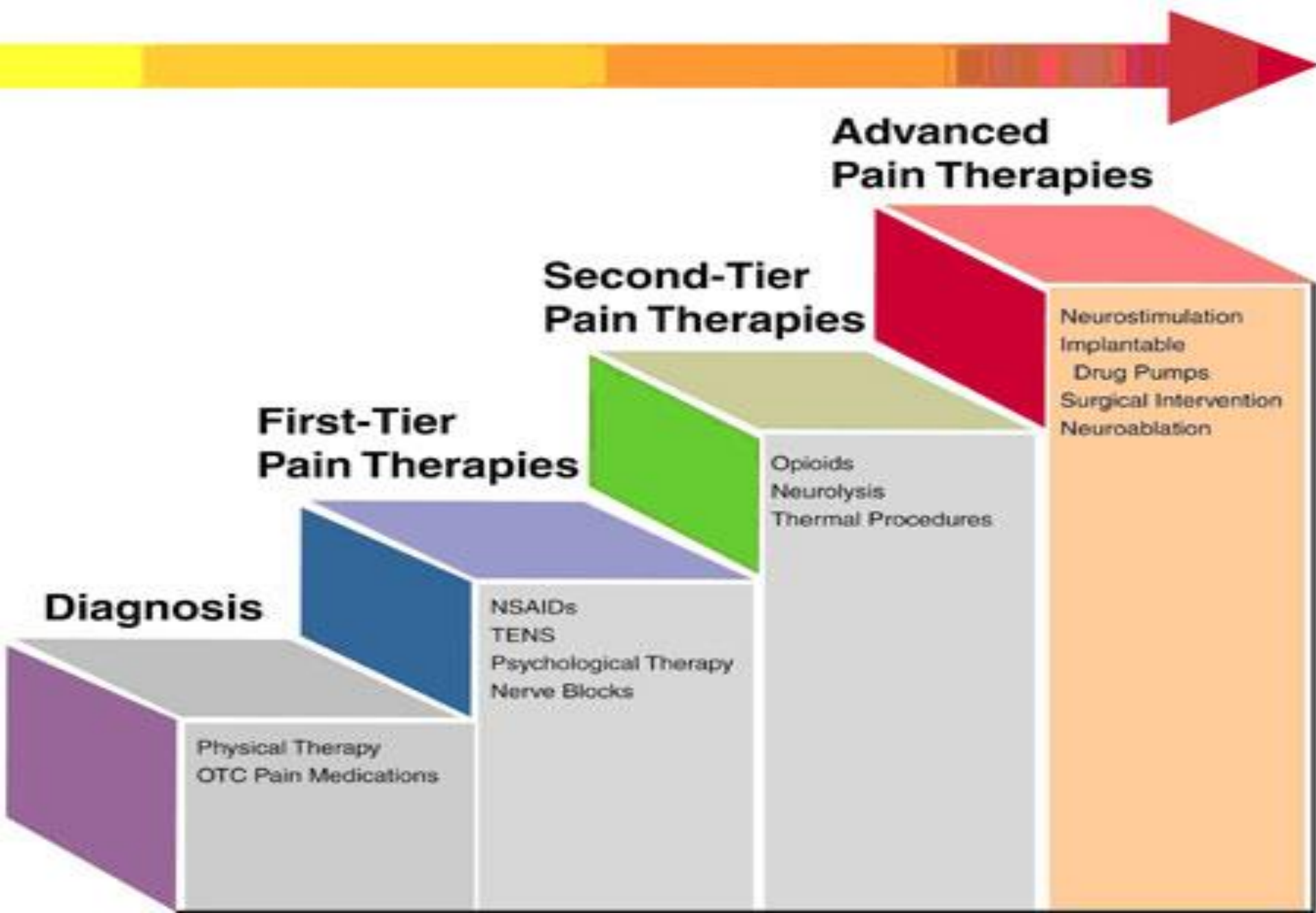
- **Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.**
- **Chronic pain is a complex phenomenon where the intensity and impact of the pain is not always directly related to pathology.**



Treatment strategy

- the underlying cause of pain should be treated whenever possible
- oral medicines are key components of pain management
- some medicines should be given regularly ("by the clock")
- therapeutic regimes need to be individualized
- monitor and evaluate for therapeutic and side effects

The Chronic Pain Treatment Continuum



Pharmacological therapy

- anticonvulsants
- antidepressants
- benzodiazepines
- *N*-methyl-d-aspartate (NMDA) receptor antagonists
- nonsteroidal anti inflammatory drugs (NSAIDs)
- opioid therapy
- topical agents

Opioid therapy

- **controlled or extended release opioid therapy (e.g., morphine and oxycodone) provides effective pain relief for patients with neuropathic pain**
- **side effects: nausea or vomiting, constipation, dizziness, somnolence, and pruritus**
- **morphine, codeine, hydrocodone, oxycodone, buprenorphine, fentanyl, methadone, tramadol, etc ...**

New therapies?

- **research done between 2005 and 2010 indicates that synthetic cannabinoids and inhaled cannabis are effective treatments for a range of neuropathic disorders**
- **opiate derivatives taken orally were found to be more effective than cannabis for most people**
- **smoked cannabis was found to relieve neuropathy associated with HIV-associated sensory neuropathy, CRPS type I, spinal cord injury, peripheral neuropathy, and nerve injury**
- **combination therapy with opioids and cannabinoids found to be synergistic in many studies from Israel**

Individualized therapy

- **we are all different in many respects and patients who suffer from PN will need to try numerous combinations of therapies before finding the one that works well to control symptoms.**
- **the underlying cause of pain should be treated whenever possible and safe to do so.**

Questions for the doctor

- **What is the evidence for the use of older medications as compared to newer ones order to achieve rapid, effective and safe pain control?**
- **What is the evidence for the use of second generation anti-epileptics (gabapentin) as compared to first generation anti-epileptics (carbamezapine) in order to achieve rapid, effective and safe pain control?**
- **What is the evidence for the use of second generation anti-epileptics such as gabapentin as compared to placebo in order to achieve rapid, effective and safe pain control?**